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Second-line treatments in benzodiazepine-resistant convulsive status epilepticus: an updated network meta-analysis including the ESET Trial – what did change?

(Letter to the Editor)

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Convulsive status epilepticus (CSE), defined as a generalized tonic-clonic seizure lasting more than 5 minutes, is a life-threatening condition, which needs to be promptly recognized to reduce the risk of long-term consequences including increased mortality and morbidity [1]. Its treatment follows a stepwise approach, with benzodiazepines representing the first-line treatment. In benzodiazepine-resistant CSE, intravenous antiepileptic drugs (AEDs) are administered.

In a recent systematic review of the literature we estimated the comparative efficacy and safety of intravenous AEDs in adults with benzodiazepine-resistant CSE; on the basis of the network meta-analysis (NMA) of the results of five trials, we concluded that high-dose phenobarbital (PHB) is effective in controlling CSE and preventing seizure recurrence, whereas lacosamide (LCM) and valproate (VPA) could be better tolerated options [2]. However, these findings were mostly driven by the very high-dose of PHB used in the included trial [3].

Recently, the results of the Established Status Epilepticus Treatment Trial (ESETT) have been published [4]. This large, high-quality, randomized controlled trial (RCT) compared levetiracetam (LEV), fosphenytoin (fosPHT) and VPA in patients with benzodiazepine-resistant CSE. These three drugs, infused over a period of 10 minutes, showed similar effectiveness and incidence of adverse events.

Taking into account the relevance of the ESETT results, we incorporated them into the previous NMA. In addition, we removed two RCTs from the initial analysis, one comparing diazepam versus VPA [5] and one comparing very high-dose PHB (20 mg/Kg as loading dose) versus VPA [3] in order to compare only AEDs (i.e., excluding benzodiazepines) used at dosages within the range proposed by the American Epilepsy guidelines and usually administered in clinical practice [6]. Efficacy outcomes were CSE cessation within 1 h from drug administration and seizure freedom at 24 h. Safety outcomes included respiratory depression and hypotension. Effect sizes were estimated by NMA within a frequentist framework. The hierarchy of competing interventions was established using the surface under the cumulative ranking curve (SUCRA) and mean ranks.

Four RCTs were considered, involving 594 patients. Included interventions were: VPA (20-40 mg/kg), PHT (20 mg/kg), fosPHT (20 mgPE/Kg), LCM 400 mg, and LEV (20-60 mg/kg). No difference was found for the occurrence of CSE cessation, seizure freedom at 24 hours, respiratory depression and hypotension. According to SUCRA, VPA had the greatest

probabilities of being best in the achievement of CSE control and seizure freedom, and the lowest probability of respiratory depression; LCM had the lowest probability of hypotension (Table 1).

Network meta-analyses cannot replace direct head-to-head comparative trials but may provide some evidence about the relative efficacy and safety of drugs [Brigo et al., 2019a]. Although no difference was found in any direct comparison between the five AEDs assed, this updated NMA could offer useful clinical information about the hierarchy of competing interventions. Results should be read with some caution due to the risk of clinical heterogeneity (ESETT included both adults and children; 61% of patients were aged ≥18 years). Additional efforts are required to estimate the comparative effectiveness of *traditional* versus *newer* AEDs, for which increasing evidence exists about their role in the treatment of status epilepticus [7,8].

Disclosures / Conflict of interest

Francesco Brigo has acted as a paid consultant to Eisai and LivaNova, and received travel support from Eisai. Eugen Trinka has acted as a paid consultant to Eisai, EVER Neuro Pharma, Biogen Idec, Medtronics, Bial, and UCB and has received speakers' honoraria from Bial, Eisai, Boehringer Ingelheim, Biogen, Newbridge, Novartis, and UCB Pharma in the past 3 years. Eugen Trinka has received research funding from UCB Pharma, Biogen, Novartis, Bayer, Eisai, Red Bull, Merck, the European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, and Bundesministerium für Wissenschaft und Forschung. Eugen Trinka is also part of the investigators planning the ESET Trial and member of the Task Force on Classification of Status Epilepticus of the International League Against Epilepsy (ILAE). Other Authors have no conflict of interest.

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Table 1. Ranking according to SUCRA and mean rank for the efficacy and safety outcomes

Supplementary materials

Table 1. Ranking according to SUCRA and mean rank for the efficacy and safety outcomes

a) Status epilepticus cessation

Treatment	SUCRA	Mean rank
PHT	55.6	2.8
VPA	59.9	2.6
LEV	53.7	2.9
LCM	34.5	3.6
fosPHT	46.2	3.2

b) Seizure freedom at 24 hours

Treatment	SUCRA	Mean rank
PHT	69.0	1.9
VPA	69.7	1.9
LEV	25.5	3.2
LCM	35.9	2.9

c) Respiratory depression

Treatment	SUCRA	Mean rank
PHT	21.4	4.1
VPA	70.8	2.2
LEV	66.3	2.3
LCM	66.0	2.4
fosPHT	25.5	4.0

d) Hypotension

Treatment	SUCRA	Mean rank
PHT	5.8	4.8
VPA	55.9	2.8
LEV	77.5	1.9
LCM	77.8	1.9

fosPHT	32.9	3.7

Abbreviations: fosPHT=fosphenytoin, LCM=lacosamide, LEV=levetiracetam, PHT=phenytoin, SUCRA=surface under the cumulative ranking curve, VPA=valproic acid. Higher SUCRA values correspond to higher probabilities of better efficacy/tolerability.

Supplementary materials

- References of included studies
- **Table 1:** Study design, definitions of SE and details of treatments in RCTs included
- **Table 2:** Clinical characteristics of patients
- **Table 3:** Risk of bias in included RCTs
- **Table 4:** Ranking according to SUCRA for the efficacy and safety outcomes
- **Figure 1:** Network of treatment comparisons for efficacy and safety
- **Figure 2:** Interval plots for the efficacy and safety outcomes

References of included studies

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Table 1: Characteristics of included randomized controlled trials.

Study	Country	Definition(s) of status epilepticus	Participants and age	Details of benzodiazepine administration	Comparators		
Agarwal et al., 2007	India	Continuous convulsive seizure > 5 min without recovery of consciousness	Adults > 18 years	DZP 0.2 mg/kg at 2 mg/min IV, max 20 mg	PHT 20 mg/kg, max rate: 50 mg/min	VPA 20 mg/kg administered at 40 mg/min	
Chakravarthi et al., 2015	India	≥2 convulsive seizures without full recovery of consciousness between seizures OR continuous convulsive seizure > 5 min	Adolescents and adults	LZP 0.1 mg/kg at 1 mg/min IV	PHT 20 mg/kg with subsequent maintenance dose (not further specified), max rate: 50 mg/min	LEV 20 mg/kg administered at 100 mg/min with subsequent maintenance dose (not further specified)	
Misra et al., 2017	India	Convulsive SE: ≥2 convulsive seizures without full recovery or continuous convulsions > 5 min. Subtle convulsive SE: coma and ictal discharges on EEG and subtle convulsive movements	Adults > 18 years	LZP 4 mg in 2-4 min IV(repeated once if seizures not controlled)	VPA 30 mg/Kg at 100 mg/min	LCM 400 mg at 60 mg/min	
Kapur et al., 2019	USA	Convulsive SE: persistent or recurrent convulsions in the emergency department at least 5 min after the last dose of benzodiazepines and no more than 30 min after the last dose of benzodiazepines	Children > 2 years	Adults and children with weight ≥32 kg: DZP 10 mg (IV or rectally), LZP 4 mg IV, or midazolam 10 mg (IV or intramuscularly). Children with weight <32 kg: DZP 0.3 mg/kg (IV or rectally), LZP 0.1 mg/kg IV, or midazolam 0.3 mg(kg (administered intramuscularly) or 0.2 mg/kg IV (administered	LEV 60 mg(Kg (maximum, 4500 mg) or	fosPHT 20 mgPE/kg (maximum, 1500 mgPE)	VPA 40 mg/kg (maximum, 3000 mg)

				intravenously)			

DZP: diazepam
fosPHT: fosphenytoin
IV: intravenous
LCM: lacosamide
LZP: lorazepam
PHT: phenytoin
SE: status epilepticus
VPA: valproate

Table 2: Clinical characteristics of patients

Study	**No of patients, sex ratio (M:F)**	**Age** **Mean age±SD [range]**	**History of previous seizures**	**Type of SE**	**Seizure duration, Mean±SD [range]**	**Etiology of SE**
Agarwal et al., 2007	***PHT group***					
	50 32:18	27±15.1 years	NR	Convulsive SE 100%	<2h in 52% of patients	AED withdrawal/noncompliance 28% Neurocysticercosis/tuberculoma 24% CNS infections 24% Primary generalized seizure 12% Stroke 4% Chronic renal failure 4% Eclampsia 4%
	VPA group					
	50 35:15	27.4±16.8 years	NR	Convulsive SE 100%	<2h in 60% of patients	AED withdrawal/noncompliance 24% Neurocysticercosis/tuberculoma 24% CNS infections 20% Primary generalized seizure 16% Stroke 4% Extradural hematoma 4% Juvenile myoclonic epilepsy 4% Brain metastasis 4%
Chakravarthi et al., 2015	***PHT group***					
	22 15:7	31.82±12.68 years	63.6%	Convulsive SE 100%	72.05±48.57 min	Idiopathic 31.8% Acute symptomatic 13.6% Remote symptomatic 54.5%
	LEV group					

	22 12:10	39.00±18.40 years	77.2%	Convulsive SE 100%	55.91±73.75 min	Idiopathic 27.3% Acute symptomatic 45.5% Remote symptomatic 27.3%
Misra et al., 2017	***LCM group***					
	33 21:12	40 [18-90] years		Generalized convulsive SE 90.9% Subtle convulsive SE 9.1%	2 hours (median) [0.08-160]	CNS infections 33.3% Stroke 30.3% Othrs 36.4%
	VPA group					
	33 25:8	40 [18-85] years		Generalized convulsive SE 97% Subtle convulsive SE 3%	2 hours (median) [0.08-60]	CNS infections 33.3% Stroke 18.2% Others 48.5%
Kapur et al., 2019	***LEV group***	33.3±26.0 [1-94]years	66.9%	Convulsive SE 100%	62.0 (43.0–85.0) min	NR
	145 77:68					
	fosPHT group	32.8±25.4 [1-84] years	67.8%	Convulsive SE 100%	59.0 (43.0–94.0) min	NR
	118 71:47					
	VPA group	32.3±25.4 [1-85] years	68.6%	Convulsive SE 100%	61.5 (38.5–86.5) min	NR
	121 65:56					

AED: antiepileptic drugs

CNS: central nervous system

h: hour(s)

min: minute(s)

NR: not explicitly reported

SD: standard deviation

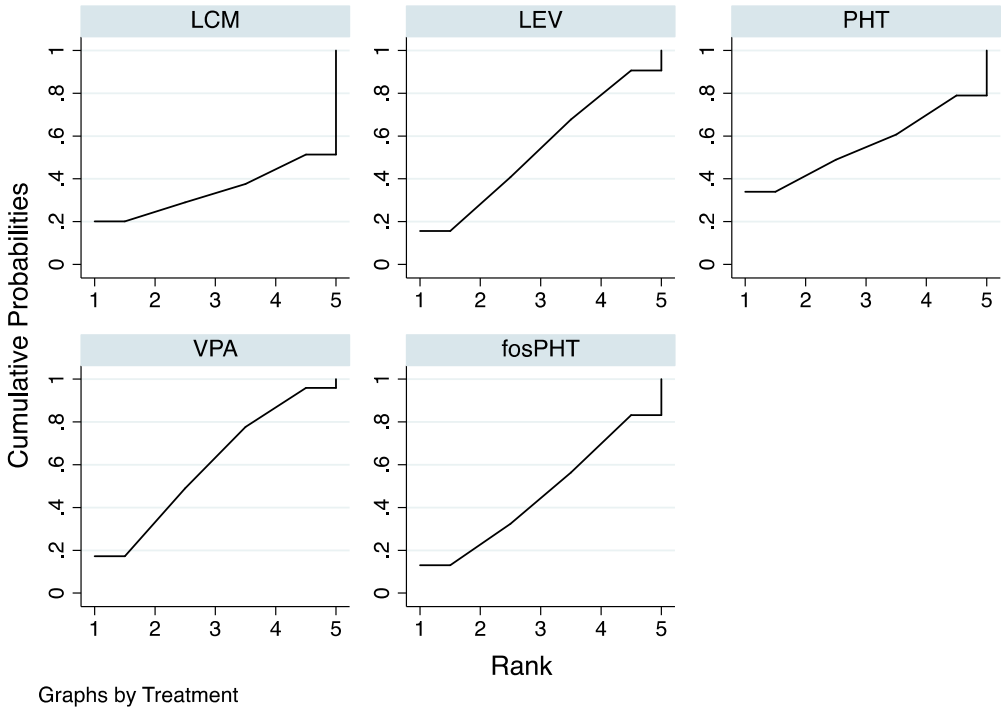
SE: status epilepticus

Table 3: Risk of bias in included randomized controlled trials

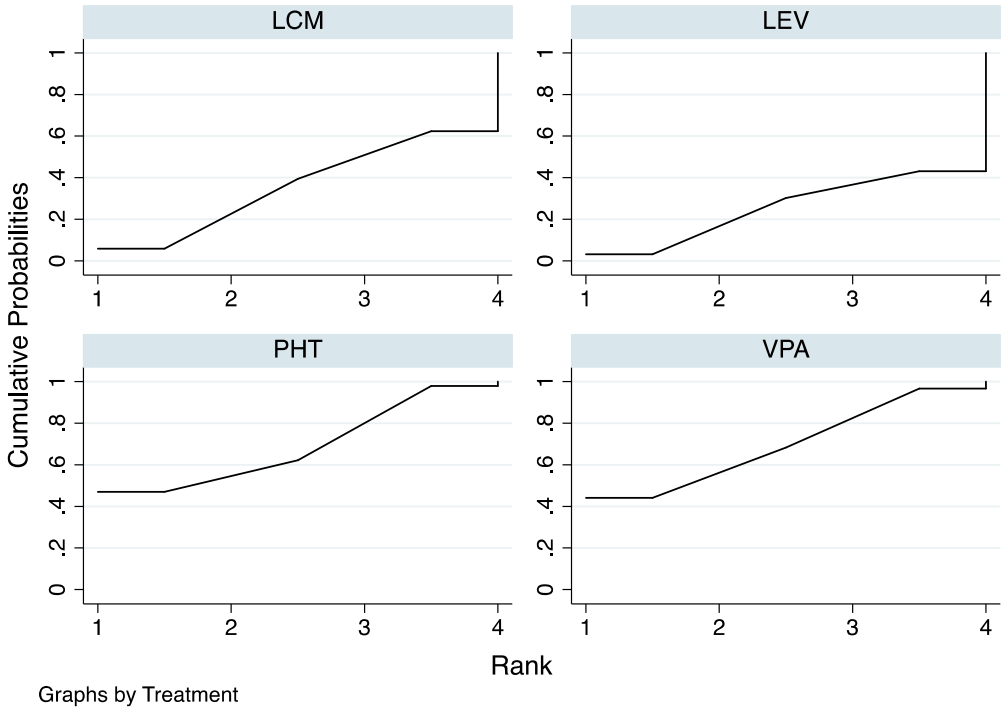
Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Agarwal et al., 2007	Unclear risk (not described)	Unclear risk (not described)	Unclear risk (not described)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Unclear risk (insufficient information to permit judgement)
Chakravarthi et al., 2015	High risk (Sequence generation depending on the order of recruitment)	High risk (open random allocation schedule)	High risk (no blinding)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Unclear risk (insufficient information to permit judgement)
Misra et al., 2017	Low risk (use of computer-generated random numbers)	Unclear risk (not described)	High risk (no blinding)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Unclear risk (insufficient information to permit judgement)
Kapur et al., 2019	Unclear risk (not clearly described)	Unclear risk (not clearly described)	Low risk (drugs identical in appearance, formulation, packaging, and administration)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Low risk

Table 4: Ranking according to SUCRA for the efficacy and safety outcomes

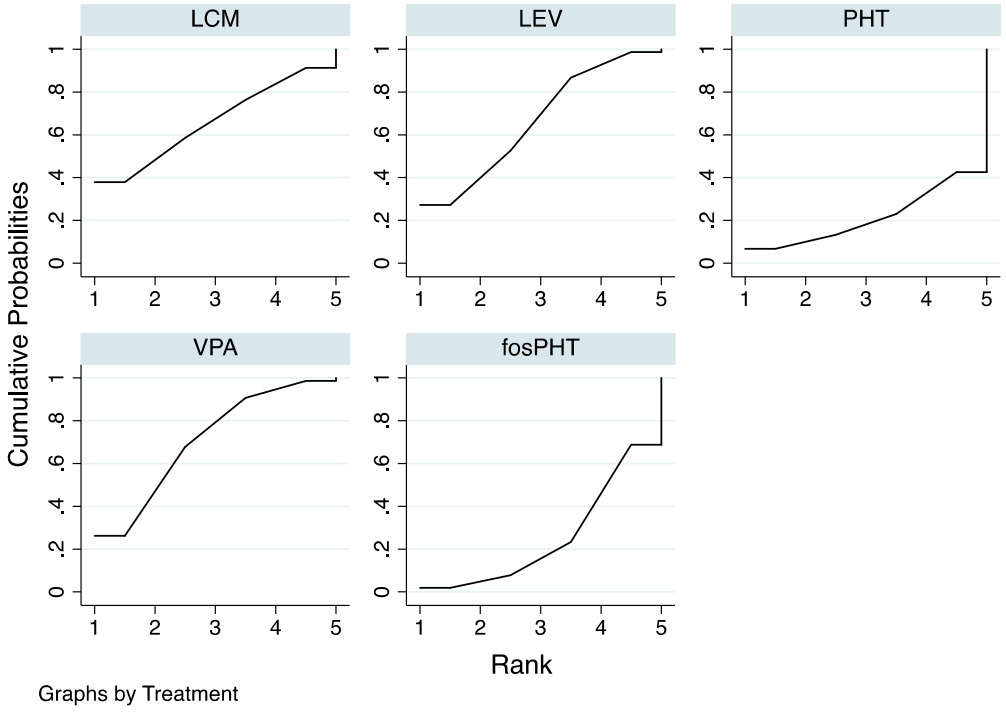
a) Status epilepticus cessation



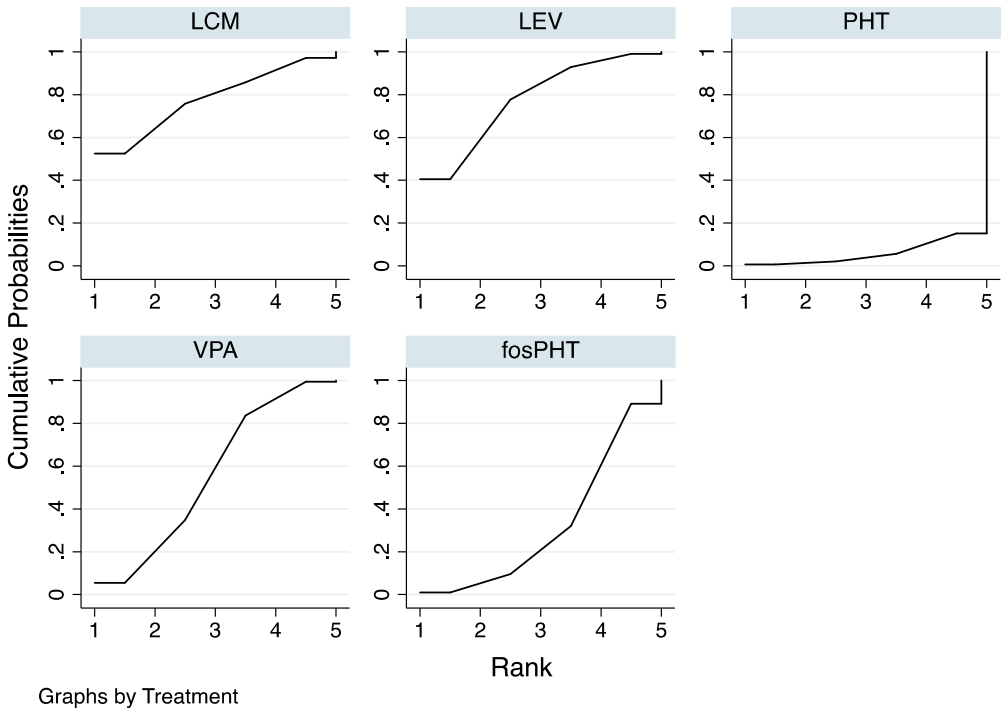
b) Seizure freedom at 24 hours



c) Respiratory depression



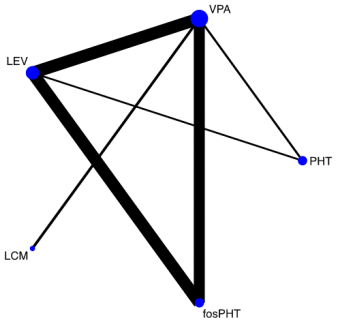
d) Hypotension



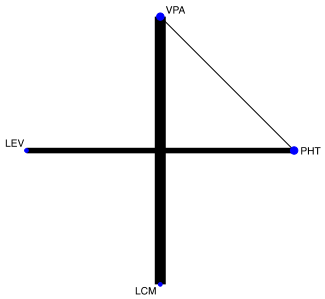
SUCRA=surface under the cumulative ranking curve.

Figure 1. Network of treatment comparisons for efficacy and safety

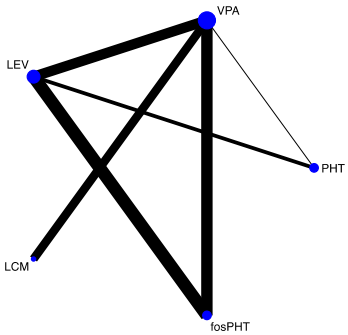
a) Status epilepticus cessation



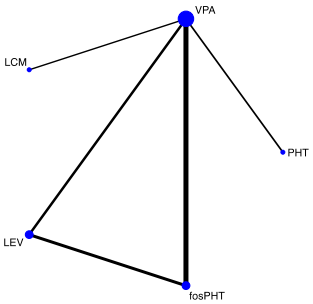
b) Seizure freedom at 24 hours



c) Respiratory depression



d) Hypotension

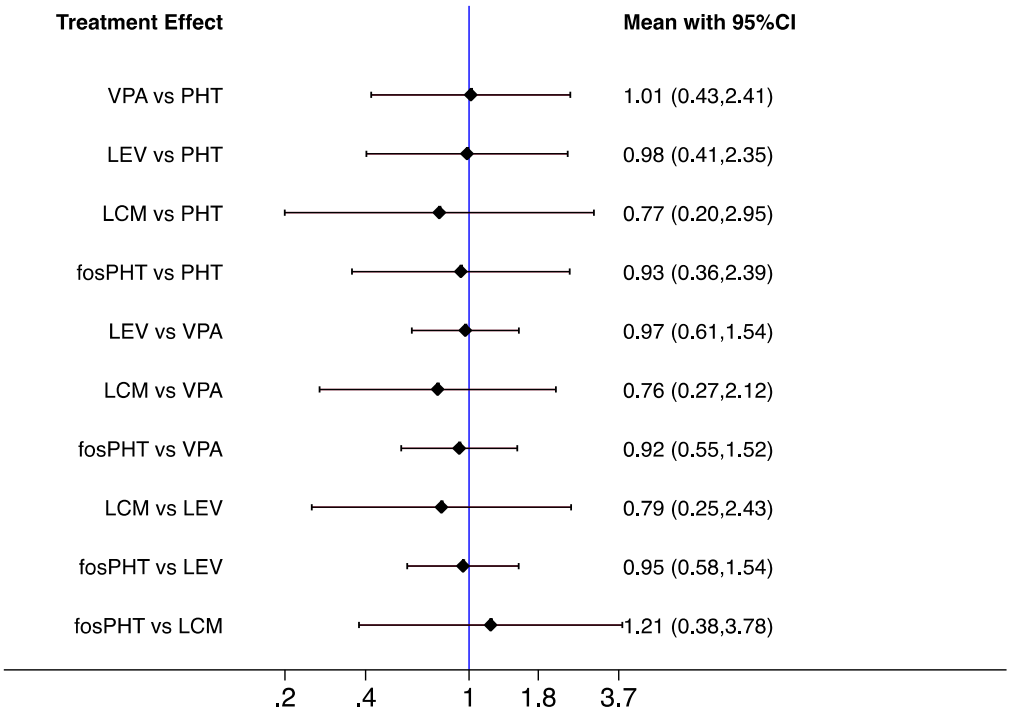


The width of the lines is proportional to the inverse of the variance of the comparison treatment effect and the size of every circle is proportional to the number of randomly assigned participants.

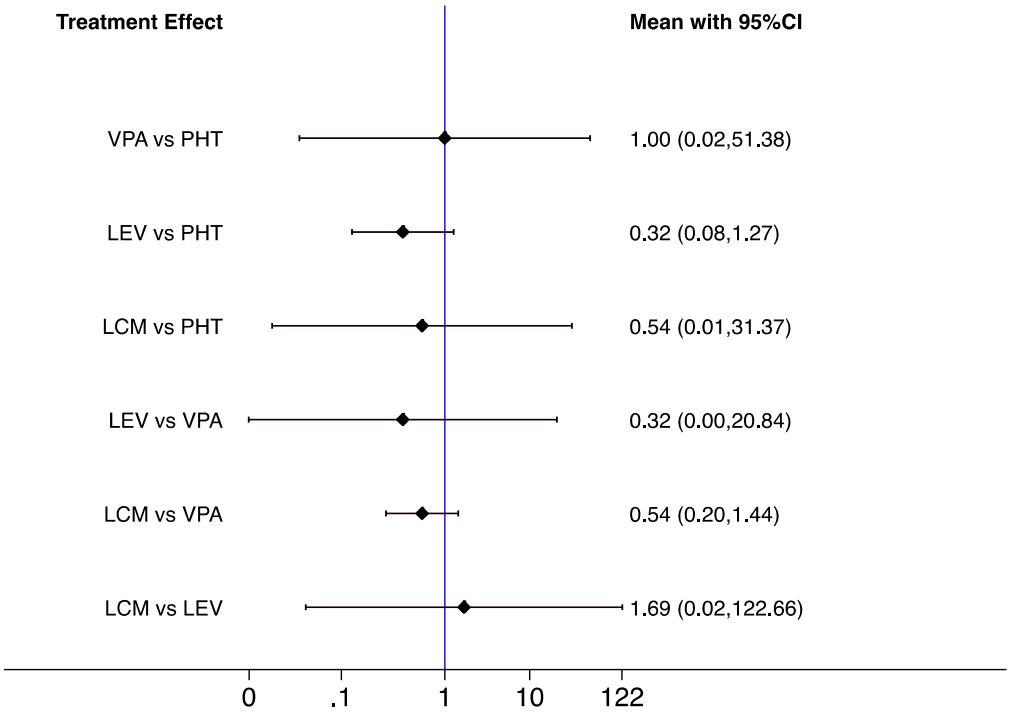
Abbreviations: fosPHT=fosphenytoin, LCM=lacosamide, LEV=levetiracetam, PHT=phenytoin, VPA=valproic acid.

Figure 2. Interval plots for the efficacy and safety outcomes

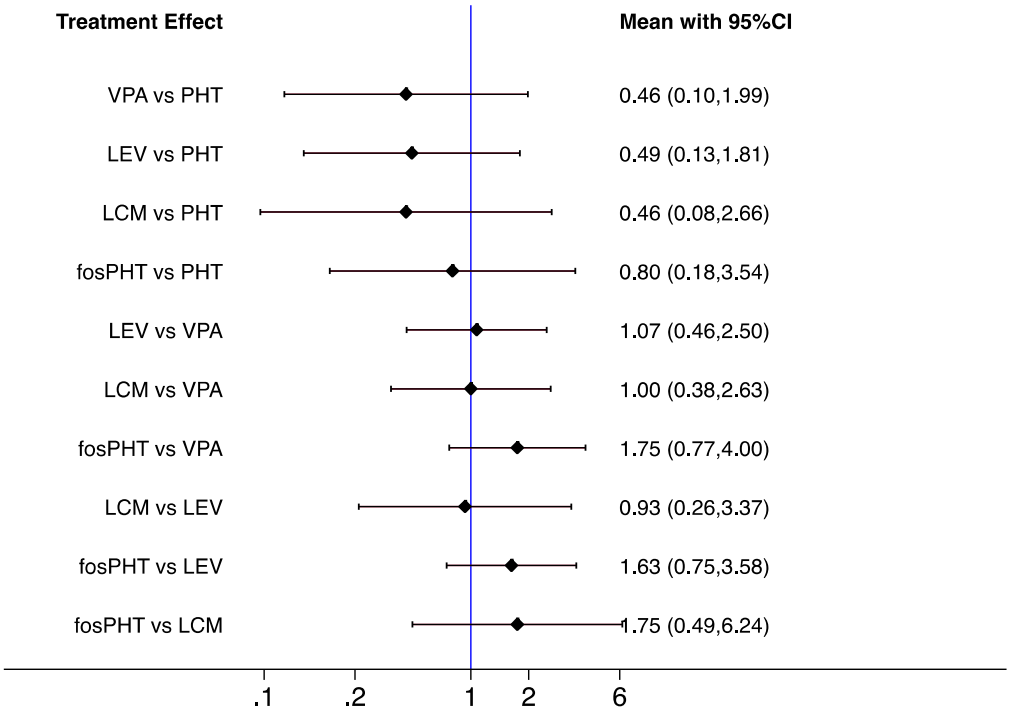
a) Status epilepticus cessation



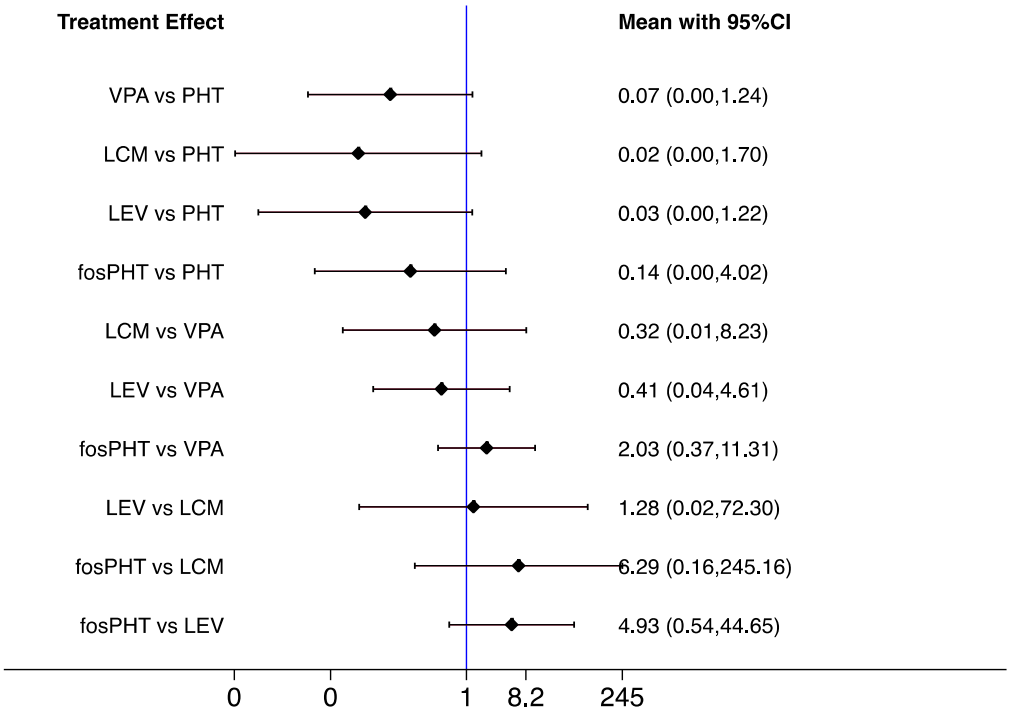
b) Seizure freedom at 24 hours



c) Respiratory depression



d) Hypotension



Abbreviations: CI=confidence interval, fosPHT=fosphenytoin, LCM=lacosamide, LEV=levetiracetam, PHT=phenytoin, VPA=valproic acid.